REMARKS

Claim 1 has been amended to recite that the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm. Support for this language can be found, for example, at page 5, last paragraph. Additionally, the features of "composite of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite" are disclosed, for example, in Example 3 on page 12, second paragraph of the specification. No new matter has been added.

The Examiner again points to the Merriam-Webster Dictionary definition of "Mineralize". Generally speaking, terms are given their plain meaning, unless the term has a particular meaning within the specification and/or the inventor has chosen to be his/her own lexicographer and give the term a special meaning. Applicants meaning of the term mineralize can easily be determined by examining the specification that clearly shows that the mineralized collagen matrix is constructed in the form of layers. At least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite. Crystals of hydroxyapatite having a length of about 300 to 500 nm are present on and between the collagen fibrils. Based on the many descriptions of the microscopic examinations found in applicants' specification, the meaning of the term "mineralized" according to applicants definition would be clear to one skilled in the art who would not look to a general purpose dictionary for a biomedical definition. Applicants' consistently use the term "mineralized" in the context of a bone analogous coating.

Rejections under 35 U.S.C. 112

Claims 1-8, 10-19, 21 and 23-27 stand rejected under 35 U.S.C. 112, first paragraph and claims 2-3 and 23 stand rejected under 35 U.S.C. 112, second paragraph. It is believed that the amendments to the claims render the rejection moot.

Claim 1 has been amended to clarify that *at least one of said layers* comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite. See, for example, page 12, lines 10-17 of the specification. Claim 2 has been cancelled and the dependency of claim 23 has been amended to depend from claim 1. At the

Examiner's suggestion, claim 3 has been amended to clarify that the collagen matrix further contains octacalcium phosphate ($Ca_8H_2(PO_4)_6\ 5H_2O$), brushite ($CaHPO_4\ 2H_2O$) or mixtures thereof.

Thus, it is respectfully requested that the rejections under 35 U.S.C. 112 be withdrawn.

Rejection under 35 U.S.C. 103

Shirkanzadeh (US 5,205,921) teaches an electrochemical process for the deposition of bioactive material made of calcium phosphate on metallic implants. The deposited calcium phosphate layer exhibits a network of non-oriented crystals. Previously presented Figure 2 shows the FTIR spectra of a calcium phosphate layer synthesized according to the method of Shirkanzadeh. The resulting structure does not resemble native bone analogous material. The coating process of Shirkanzadeh may also be carried out in the presence of biological molecules like collagen. Shirkanzadeh teaches a formed calcium phosphate layer characterized by calcium phosphate crystal sizes of approximately 20 μm (Example 1 of Shirkanzadeh) or 2 to 5 μm (Example 2 of Shirkanzadeh). A crystal size of 2 to 20 μm (i.e., 2000-20,000 nm) does not promote the formation of collagen - calcium phosphate interconnected layers; the calcium phosphate particles according to Shirkanzadeh are simply too large.

As can be seen in enclosed pp. 173 of Lehninger "Principles of Biochemistry", collagen is a rod-shaped molecule of about 3,000 Å long (300 nm) and 15 Å thick. In order to form bone analogous structures of interconnected layers, the calcium phosphate crystallite growth has to occur on and between the collagen fibrils. Thus, in bone analogous structures the hydroxyapatite crystals must be small enough to interact within the collagen fibrils which have a size of about 0.3 μm or 3000 Å. Hydroxyapatite crystals of a size between 2 to 20 μm (i.e., 2000-20,000 nm) as taught by Shirkanzadeh (see Examples 1 and 2) are much too large to grow on and between collagen fibrils. Using hydroxyapatite crystals of a size much larger than collagen fibrils would result in domination of the mineral component, thereby creating a simple admixture of the collagen into the mineral matrix.

Shirkanzadeh is silent regarding a coated metallic implant with an outer layer of a bone analogous coating comprising a collagen matrix which is constructed in layers wherein at least one of these layers comprises a composite of mineralized collagen fibrils, amorphous calcium

phosphate and crystalline hydroxyapatite. Shirkanzadeh is particularly silent regarding hydroxyapatite crystals having a length of about 300 to 500 nm (i.e., 0.3 to 0.5 μm), and, in fact, suggests the use of much larger crystals.

Liu et al. describes a strong, flexible, mineralized collagen membrane and a method of making the same. The membrane comprises a homogeneous mineralized collagen composite of 30 to 70 wt% of a collagen component and 30 to 70 wt% of a calcium phosphate component. The membrane is produced by precipitation of calcium phosphate mineral in a collagen slurry by maintaining a pH of at least 7.0. Liu et al. utilizes an electrolyte solution of different salt concentrations and the precipitation processes causes the formation of different calcium phosphate-collagen compositions. As noted in Example 1 of Liu et al., the precipitation of calcium phosphate mineral is induced immediately after mixing a 500 mM calcium ion containing solution and a 500 mM phosphate ion containing solution to the collagen slurry at a pH of about 9. This results in the immediate precipitation of calcium phosphate. Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Thus, only a very loose network of calcium phosphate crystals and collagen fibrils is formed. Moreover, Liu et al. does not disclose or suggest the use of hydroxyapatite crystals having a length of about 300 to 500 nm.

In this rejection, Liu et al. is relied on as a teaching of using different types of clacium phosphate in a mixture. However, there is not suggestion of using such mixtures in the electrochemical process of Shirkanzadeh. Dispersed particles, of calcium phosphate mineralized collagen, as taught by Liu, cannot be precipitated in an electrochemical process. An electrochemical precipitation process requires imperatively charged particles. A calcium phosphate mineralized collagen according to Liu does not possess an electrical charge anymore. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant according to the invention.

Thus, the combined teachings of Shirkanzadeh and Liu et al would not lead one skilled in the art to an implant with the features of the claimed invention. Shirkanzadeh only teaches a method for forming a single layer of hydroxyapatite on the surface of a metallic implant and Liu

et al. is silent regarding a metal surface of a metallic implant. Shirkanzedah and Liu are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm.

Kwan et al. discloses a three-dimensional bone grafting matrix comprising mineralized fibrillar insoluble collagen, collagen derivatives or modified gelatin. The matrix is obtained by mixing fibrillar collagen with calcium chloride and tribasic sodium phosphate at a pH of 11. After mineralization, the collagen is combined with a binder in form of soluble collagen, gelatin, polylactic acids and others. See, for example, column 4, lines 13 through 20 of Kwan et al. The resultant calcium phosphate is immobilized within the matrix and comprises particles of an average diameter of about 3 to 5 μm (3000 to 5000 nm). Kwan mentions that the particle size might be less than 3-5 μm. However, nothing in the teaching of Kwan would direct one skilled in the art to arrive at a particle size ten fold smaller then the range provided. Further, as discussed above, one of ordinary skill in the art would not look to a process, such as described by Kwan et al., to modify an electrodeposition process such as disclosed by Shirkanzadeh. Furthermore, Kwan teaches a calcium chloride solution having a concentration of 50mM and a sodium phosphate solution having a concentration of 30 mM for the formation of the matrix. Kwan teaches at least a 30 fold higher salt concentration than the electrochemical precipitation process of the present invention. As with Liu et al. discussed above, this would cause immediate precipitation of the calcium phosphate, thus, forming calcium phosphate crystals of about 3 to 5 μm (3000 to 5000 nm).

Sauk et al. teaches a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphophoryn calcium salt and type I collagen for application in osseous repair. Exposing the composite of Sauk et al. to a coating process according to Shirkanzadeh would not result in an implant according to the claimed invention. Like Liu and Kwan discussed above, the composition of Sauk et al. does not posses electrochemical charges promoting electrochemical migration and precipitation. Moreover, Sauk et al. does not teach or suggest a mineralized

collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm.

Rhee et al. discloses implants coated with a collagen-polymer-conjugate. The Examiner points to Example 7 of Rhee, which allegedly teaches the same components as the claimed invention and allegedly must have the same properties as the instant invention. However, Rhee et al. discloses implants coated with a collagen-polymer-conjugate created by simply dipping the implant in a collagen-polymer solution. See, for example, Example 5 of Rhee. Such a dipping provides a collagen matrix coating that does not strongly attach to an implant. The Examiner states that it would have been obvious to use a composition according to Example 7 of Rhee et al. to coat an implant. Example 7 provides a solid formulation of cross-linked collagen or collagen derivatives with hydroxyapatite and tricalcium phosphate by admixing collagen with hydroxyapatite and tricalcium phosphate. Thus, calcium phosphate crystals are used right from the start and are not formed during the mixing process. Such a simple mixing does not lead to a strong attachment of the crystals to the collagen fibrils, let alone to the specific crystal size of the present invention. Additionally, the solid formulation of Example 7 of Rhee et al. would not posses an electrochemical charge suitable for supporting an electrochemical migration and precipitation process.

Worch et al. describes a metallic object with a polyphase oxide coating having a metal oxide phase and at least one other organic and/or inorganic phase. The organic phase can contain collagen and the inorganic phase can contain calcium phosphate. Due to the anodic coating process the inorganic and/or organic phase are embedded or incorporated into the metal oxide phase of the implant. The inorganic phase does not form multiple layers on the implant surface.

One skilled in the art would find no teaching or suggestion in Worch of an implant coated with a mineralized collagen matrix comprising mineralized collagen fbrils, amorphous calcium phosphate and hydroxyapatite crystals with a length between about 300 to 500 nm. Also by combining the teachings of Worch et al. and Liu et al a person skilled in the art would not arrive at the implant of the present invention.

Thus, the teachings of Shirkanzadeh, Liu, Sauk, Kwan, Worch, and Rhee, either individually or together, do not describe or suggest a bone analogous coating comprising a mineralized collagen matrix constructed in the form of layers wherein at least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite, the latter having a length of about 300 to 500 nm.

Therefore, it is respectfully requested that the rejections under 35 U.S.C. §103 should be withdrawn.

Double Patenting rejection

The pending claims are further rejected on grounds of nonstatutory obviousness-type double patenting over claims 1 to 23 of Liu et al. (US 6,300,315, Liu et al).

The claims of Liu et al. does not teach or suggest a metal surface of a metallic implant. The claims of Liu are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm.

Thus, the double patent rejection should be withdrawn.

In view of the amendments and above remarks, favorable consideration is courteously requested. However, if there is any remaining issue(s) which can be expeditiously resolved by a telephone conference, the Examiner is courteously requested to telephone the undersigned at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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